8 Papers

Paper I

ORIGINAL ARTICLE EPID

Allergic disease and *Staphylococcus aureus* carriage in adolescents in the Arctic region of Norway

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Keywords
allergic disease; allergic multimorbidity; allergic rhinitis; asthma; eczema; *Staphylococcus aureus*

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Abstract

Background: Allergic diseases are common chronic diseases in children and adolescents, but limited epidemiological data are available during transition into adulthood. Nasal *Staphylococcus aureus* carriage has been linked to increased prevalence of allergic disease. The objective of this study was to define the prevalence of allergic diseases in adolescents above the Arctic Circle in Northern Norway and to study the associations of *S. aureus* carriage with allergic diseases.

Methods: A school-based cohort in late adolescence (18–19 years) was invited to participate in a cross-sectional study on lifestyle and health, and 868 attended (71.9%). Self-reported allergic disease and severity of eczema were assessed by Mechanisms of the Development of Allergy and Patient-Oriented Eczema Measure questionnaires. Participants were tested with spirometry and exhaled nitric oxide (FeNO) and swabbed for bacterial culture from nose and eczematous skin.

Results: We found asthma, eczema, allergic rhinitis (AR), and nasal *S. aureus* carriage among 11.9%, 10.4%, 26.0%, and 51.3% of the participants, respectively, and 10.2% had allergic multimorbidity. Lifetime prevalence for any allergic disease was 45.1%. Reduced lung function and increased FeNO were found in 11.6% and 22.1% in participants with asthma, respectively. Nasal *S. aureus* carriage was associated with eczema, severe asthma, and severe AR. FeNO > 25 ppb was associated with both asthma and nasal *S. aureus* carriage.

Conclusion: Asthma, eczema, and AR are common among adolescents above the Arctic Circle in Norway. Allergic disease is associated with *S. aureus* carriage, but its role in the pathogenesis and severity is not established.

In Northern Norway, gradually increasing prevalence of eczema, asthma, and allergic rhinitis (AR) was shown among schoolchildren age 7–14 years in three surveys between 1985 and 2008, reaching 17.6% for asthma ever and 43.3% for any allergic disease ever in the last survey (1). Hitherto, there has been limited data on the prevalence of allergic diseases in late adolescence and during transition into adulthood, both in the Arctic regions and internationally. However, three European birth cohort studies recently published epidemiological follow-up data: the British Isle of Wight (IoW) study up to 18 years of age (2), the German Multicentre Allergy Study (MAS) up to 20 years of age (3), and the Swedish BAMSE study up to 16 years of age (4).

The role of infections and bacterial carriage in the pathogenesis of allergic diseases is unclear. Some studies indicate that *Staphylococcus aureus* toxins are involved in allergic inflammation (5–8). The nose, throat, and skin are the major sites of *S. aureus* carriage (9). Patients with AR have a higher nasal carriage rate of *S. aureus* associated with aggravation of AR symptoms, possibly by promoting local IgE production to staphylococcal super antigens (10, 11). There are conflicting data on a possible association between *S. aureus* carriage and

asthma. In infants and preschool children, no clear association between *S. aureus* carriage and wheeze or airway inflammation has been shown so far (12). However, in older children and adolescents, *S. aureus* nasal carriage has been associated with increased risk of asthma and asthma exacerbations (13).

Few studies have examined the prevalence of allergic disease and their association with *S. aureus* carriage in late adolescence. The aims of our study were firstly to describe the prevalence of allergic disease among adolescents above the Arctic circle in Northern Norway and secondly to analyze associations between nasal *S. aureus* carriage and allergic diseases.

Methods

Sample

The Tromsø Study Fit Futures (TFF) cohort was initiated in 2010–2011. All first-year high school students in both academic and vocational educational programs from all 8 high schools in the municipalities of Tromsø and Balsfjord were invited to participate (TFF1) and 92.8% attended (14). In this region, more than 90% of the population in the age group 16-19 years attend high school. In the second wave of the study (2012–2013), all third-year high school students, including all participants from TFF1, were invited for follow-up (TFF2). Among 1208 invited students, 868 (71.9%) participated in TFF2. Each participant completed a web-based general health and lifestyle questionnaire (http://www.questback.com) and underwent clinical examination during a 1-day session, between November 2012 and June 2013. Among the 868 participants, 844 (97.2%) answered the questionnaire. A total of 825 (95.1%) underwent clinical examinations, 812 (93.5%) measured fractional exhaled nitric oxide (FeNO), and 804 (92.6%) performed spirometry with reversibility test. Another 819 (94.4%) participants had a nasal swab performed for analysis of *S. aureus* carriage, and samples for identification of *S. aureus* were successfully taken from eczematous skin in 46 of 63 participants with eczema on the day of visit.

Definition of allergy related disease outcomes

The Mechanisms of the Development of Allergy (MeDALL) core questionnaire for adolescents (15) was incorporated in the web-based questionnaire. The MeDALL questionnaire was translated from Swedish to Norwegian and back-translated in good agreement with the original Swedish and English versions. The classification of allergic diseases was based on standardized self-reported questions (MeDALL) used by European population-based birth cohort studies on asthma and allergy and validated in the International Study of Asthma and Allergies in Childhood (ISAAC) (15). Outcome definitions of allergic diseases are listed in Table 1.

Participants with eczema on the day of visit answered the Patient-Oriented Eczema Measure (POEM) questionnaire, a simple, valid, repeatable, and readily understandable tool for monitoring disease severity in children and adults (16). The gradings for POEM scores are as follows: 0–2 (clear/almost clear); 3–7 (mild); 8–16 (moderate); 17–24 (severe); 25–28 (very severe) (17).

Fractional exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) was measured with NIOX MINO® (Aerocrine AB, Solna, Sweden) with one measurement for each participant in the sitting position before performing spirometry (18).

Spirometry with reversibility test

Lung function was measured with the Easy On-PC Spirometry System (Medizintechnik AG, Zürich, Switzerland) in the sitting position. The best result of approved tests (minimum 2) was used in the analysis. Decision on approval was taken by trained assistants performing spirometry. Questionnaire data were blinded to the assistants. Reversibility was tested using 0.2 mg salbutamol inhalation aerosol (Airomir Autohaler®, Teva UK Limited, Eastbourne, UK). Post-reversibility spirometry was performed 15–25 min after the salbutamol inhalation. The Global Lungs Initiative (GLI 2012) equations were used as reference for spirometry (19). Spirometry data were anonymized at analysis.

Assessment of *S. aureus* carriage – nose and skin

Using a NaCl-moistened sterile rayon-tipped swab, we swabbed both anterior nares (taking care to avoid skin contact) in 819 participants and eczematous skin areas in 46 participants with active eczema. The eczematous skin was rubbed with a NaCl-moistened compress prior to swabbing. *S. aureus* was identified using methods previously described (20) with a few modifications; all swabs were submerged into Bacto® m Staphylococcus medium broth (Difco laboratories, Sparks, MD, USA) for enrichment and incubated for 18–24 h at 37°C before plating. The liquid culture was then plated on blood agar (Oxoid, Cambridge, UK) and *S. aureus* ID agar (SAID, bioMérieux, Marcy I′Etoile, France) and incubated for 18-24 hours at 37°C. The most dominating colony was selected and confirmed as *S. aureus* by the Staphaurex Plus (Remel, Lenexa, KS, USA) agglutination test. Only observations of bacterial growth on blood agar (Oxoid, Cambridge, UK) and/or SAID agar (BioMérieux, Marcy I′Etoile, France) plates were included. We defined a positive *S. aureus* culture result as *S. aureus* carriage. We did not perform quantitative analysis of bacterial load.

Statistical methods

Statistical analyses were performed with IBM SPSS statistics, version 21 (North Castle, New York, USA). The characteristics of the study participants and prevalence of symptoms of allergic diseases were described with summary statistics. Pearson's chi-square test and Student's t-test were used in univariate comparisons of categorical and continuous variables, respectively. Mann–Whitney U-test was used for univariate comparisons of non-normally distributed continuous data. Multivariable

Table 1 Clinical outcome definitions, The Tromsø Study Fit Futures 2

	Current	Ever	Severe
Eczema	Dry skin, itchy rashes with age-specific location (antecubital or popliteal fossae, wrists, ankles, neck or face) for 2 weeks or more in the past 12 months, or self-reported eczema combined with us of topical corticosteroids in the past 12 months (4).	Current eczema or self-reported doctor-diagnosed eczema ever	Current eczema and eczema duration more than 1 month last 12 months or kept awake due to itchy rash during nights
Asthma	At least two of the following 3 criteria: 1) self-reported doctor-diagnosed asthma ever, 2) any indicative symptom in the last 12 months (wheezing, shortness of breath, dry cough at night), and 3) us of asthma medication in the past 12 months (3).	Current asthma or self-reported doctor-diagnosed asthma ever	Current asthma and FeNO > 25 ppb or breathing difficulties last 12 months graded 7–10 on a scale from 0 (no complaints) to 10 (the hardest to imagine) and more than 12 attacks with wheeze/breathing difficulties last 12 months.
Allergic Rhinitis (AR)	Symptoms of sneezing, a runny or blocked nose, or itchy, red, and watery eyes after exposure to furred pets or pollen the last 12 months (4).	Current rhinitis or self-reported doctor-diagnosed allergic rhinitis ever	Current AR and use of nose spray last 12 months or nose symptoms more than 4 weeks in a row last 12 months or nose complaints graded 7–10 on a scale from 0 (no complaints) to 10 (the hardest to imagine) or having to stop activity due to nose problems or disturbed sleep due to nose problems
Multimorbidity	Having at least two of the diseases current eczema, current asthma, or current AR (4).	Current multimorbidity or at least two of self-reported doctor-diagnosed eczema or asthma or allergic rhinitis ever	

logistic regression models were used to analyze associations between nasal *S. aureus* colonization and allergic diseases, including relevant co-variables (21, 22). The frequencies of the three major allergic diseases and their overlap were presented in Venn diagrams. For drawing of proportional Venn diagrams, Euler APE was used (http://www.eulerdiagrams.org/eulerAPE) (23). Statistical significance was assumed at a 5% level.

Ethics

Informed consent was signed by each participant in TFF2. The study was approved by the Regional Committee for Medical and Health Research Ethics.

Results

General characteristics of study participants

Among 868 participants, the mean age was 18.6 years and 26% were overweight (BMI $\geq$ 25 kg/m^2) (Table 2). Men had more overweight, used more snuff tobacco, and had more screen-time than women.

Prevalence rates for allergic diseases

Table 3 shows the current (last 12 months) and lifetime prevalence for allergic diseases and multimorbidity. Women had higher current and lifetime prevalence for eczema and higher prevalence of current allergic multimorbidity. Fig. 1 shows the overlapping prevalence of asthma, AR, and eczema. Asthma (55%) and eczema (57%) were more common in conjunction with other allergic diseases than occurring as single entities. In contrast, AR (62%) more frequently occurred as a single entity.

Asthma medication

Among participants with asthma, over the last 12 months 86% were treated with short-acting β-2 agonists, 66% with inhaled corticosteroids (ICS) alone or in combination with long-acting β-2 agonists (LABA), 17% with LABA, and 15% with leukotriene receptor antagonists.

Nasal *S. aureus* carriage and allergic disease

Nasal *S. aureus* carriage was found in 51.3% of the participants with no gender difference. Nasal *S. aureus* carriage was associated with eczema, but not asthma and AR, in multivariable logistic regression models (Table 4). *S. aureus* carriage was associated with severe eczema, severe asthma, severe AR, or having one severe allergic disease (Table 4). When adjusting for the two other allergic diseases, the associations with nasal *S. aureus* carriage remained significant for severe asthma (OR = 2.88, 95% CI = 1.10–7.55), severe eczema (OR = 2.36,

Table 2 Characteristics of the study participants. The Tromsø Study Fit Futures 2

Variable	Total	Women	Men	p-value*
Sex	868 (100%)	480 (55.3%)	388 (44.7%)	
Age, mean (SD)	18.6 (1.5)	18.6 (1.1)	18.5 (1.8)	0.464
BMI ≥ 25 kg/m^2	26.3%	22.7%	29.8%	0.025
Daily Smoking	4.6%	3.6%	5.6%	0.182
Smoking sometimes	20.4%	18.2%	22.6%	0.121
Daily use of snuff tobacco	30.0%	26.6%	33.3%	0.034
Sometimes use of snuff tobacco	9.5%	10.8%	8.1%	0.197
Physical activity outside school hours	62.3%	61.1%	63.6%	0.475
≥4 h screen-time on week days	39.0%	30.2%	47.8%	< 0.001

*Pearson's chi-square test and Student's *t*-test were used in univariate comparisons of categorical and continuous variables, respectively. BMI: body mass index. n = 868, n may vary (between 850 and 868) due to missing values. Total prevalence is adjusted for gender difference in participation rate.

95% CI = 1.20–4.63), and severe AR (OR = 1.73, 95% CI = 1.09–2.75). When adjusting for the two other severe allergic diseases, only the association between severe eczema and nasal *S. aureus* carriage remained significant (OR = 2.22, 95% CI = 1.02–4.84).

S. aureus carriage on eczematous skin and POEM score

On the day of visit, 63 of 825 participants (7.6%) had active eczema; 42 women (63.7%) and 21 men. The distribution of POEM scores is shown in Fig. 2. Eczema severity was moderate, severe, or very severe in 60.4% of the participants with eczema on the day of visit. *S. aureus* carriage was found in 23 of 46 (50%) samples from eczematous skin of whom 21 (91.3%) also had nasal carriage. Fig. 3 shows that participants with eczematous *S. aureus* skin carriage had higher POEM score (mean 14.1, SD 6.9) compared with participants without *S. aureus* skin carriage (mean 8.5, SD 4.8) (p = 0.003).

Spirometry, FeNO, and association with nasal *S. aureus* carriage

FEV_1/FVC below lower level of normal (LLN) was more frequent in asthmatic (11/95; 11.6%) vs. non-asthmatic participants (37/688; 5.4%) (p = 0.021). Mean improvement in FEV_1 after inhalation of salbutamol was 4.5% and 2.9% (p = 0.017) for asthmatic and non-asthmatic participants, respectively. Only 5 of 95 (5.3%) asthmatic participants had more than 12% improvement in FEV_1 after inhalation of salbutamol. Twenty-one of 95 (22.1%) asthmatic participants and 70 of 694 (10.1%) non-asthmatic participants had FeNO more than 25 ppb (p = 0.002). Participants with asthma had higher mean levels of FeNO (21.5 ppb, SD 16.4) compared with non-asthmatic participants (16.4 ppb, SD 13.3) (p = 0.005).

FeNO > 25 ppb was associated with both asthma (OR = 2.48, 95% CI = 1.41–4.35) and nasal *S. aureus* carriage

Table 3 Prevalence of allergic diseases in the Tromsø study Fit Futures 2 compared with studies from Sweden (4), Germany (3), and United Kingdom (2)

Allergic disease ever					Current allergic disease						
Study	Tromsø Study Fit Futures 2				Tromsø Study Fit Futures 2				BAMSE	MAS	IoW
Age in years	18–19				18–19				16	20	18
	Total*	Women	Men	p**	Total*	Women	Men	p**	Total	Total	Total
Eczema	19.1%	24.6%	13.7%	<0.001	10.4%	14.0%	6.8%	0.001	9.1%	12.9%	12.4%
Asthma	15.9%	16.3%	15.5%	0.776	11.9%	13.6%	10.3%	0.167	7.1%	13.5%	17.6%
Allergic rhinitis	28.9%	29.9%	28.7%	0.939	26.0%	26.7%	25.3%	0.693	25.9%	21.6%	35.7%
Any allergic disease	45.1%	48.0	42.3%	0.062	36.5%	39.3%	33.6%	0.096			
Multimorbidity	15.7%	17.9%	13.4%	0.086	10.2%	12.7%	7.9%	0.024	8.4%	12.1%	15.8%

In the Tromsø Study Fit Futures 2, the number of participants for the different allergic diseases varies due to missing values in the questionnaire (total n = 832–842, women n = 465–472, men n = 366–371). Current disease = 12-month prevalence. MAS = The German Multicentre Allergy Study (n = 942). IoW = The Isle of Wight birth cohort study (n = 1298). BAMSE = The Swedish birth cohort study on asthma and allergy (n = 2607). Outcome definitions are listed in Table 1.

*Total prevalence is adjusted for different participation rate among men and women.

**Pearson's chi-square test for differences between genders.

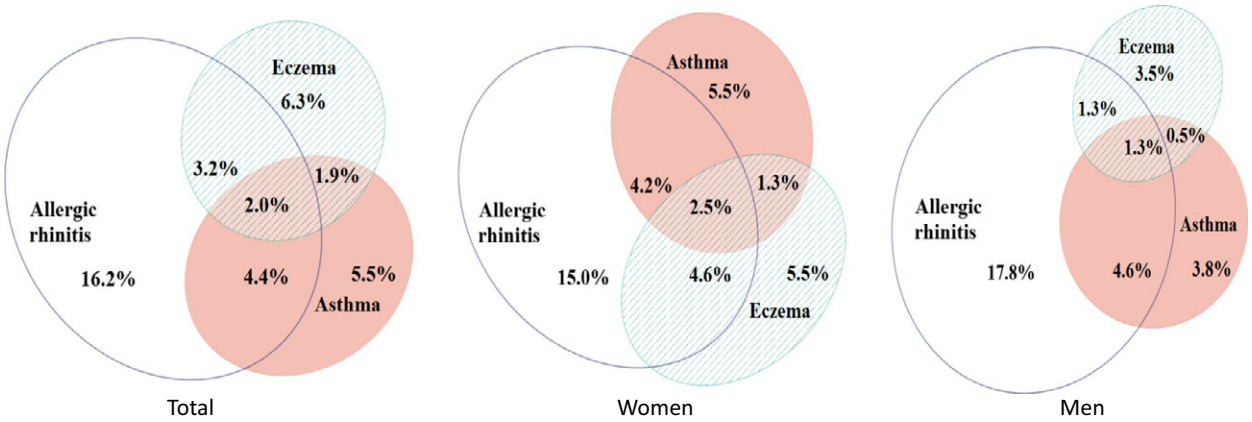

Figure 1 Area-proportional Venn diagrams showing overlapping prevalence rates for asthma, eczema, and allergic rhinitis. Total (n = 842), Women (n = 472) and Men (n = 371). The Tromsø Study Fit Futures 2.

(OR = 2.03, 95% CI = 1.26–3.24) in multivariable logistic regression models adjusted for the use of antibiotics last 3 months, sex, BMI, screen-time, physical activity, smoking, and the use of snuff tobacco. After stratification by carriage of *S. aureus*, the association between FeNO and asthma was strengthened among the carriers (OR = 3.00, 95% CI = 1.49–6.03), whereas no longer any association between FeNO and asthma was found in non-carriers (OR = 1.90, 95% CI = 0.65–5.23). FEV1/FVC below LLN was not associated with nasal *S. aureus* carriage (OR = 1.44, 95% CI = 0.79–2.63).

Table 4 Associations between allergic disease and nasal *S. aureus* carriage

	Asthma		Severe Asthma		Eczema		Severe Eczema		Allergic rhinitis (AR)		Severe Allergic rhinitis	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Univariable												
Nasal *S. aureus* carriage	1.19	0.77–1.83	3.34	1.33–8.37	1.77	1.11–2.83	2.43	1.29–4.60	1.26	0.92–1.73	1.65	1.06–2.55
Multivariable												
Nasal *S. aureus* carriage	1.17	0,75–1,82	3.47	1.37–8.82	1.79	1.11–2.91	2.49	1.29–4.80	1.24	0.90–1.72	1.71	1.09–2.66
Sex	1.38	087–2.19	1.45	0.61–3.44	2.66	1.57–4.51	3.37	1.66–6.83	1.06	0.76–1.48	1.57	0.98–2.51
BMI	1.29	0.79–2.10	1.41	0.59–3.36	1.41	0.84–2.37	1.43	0.74–2.75	0.74	0.50–1.08	0.81	0.48–1.35
Antibiotic use last 3 months	0.66	0.30–1.43	1.48	0.48–4.60	0.30	0.11–0.85	0.24	0.56–1.04	0.93	0.55–1.57	0.71	0.34–1.51
Screen–time on weekdays	1.01	0.64–1.61	1.11	0.48–2.57	1.04	0.63–1.71	1.17	0.63–2.20	0.92	0.65–1.29	1.02	0.65–1.62
Physical activity outside school time	1.39	0.86–2.23	0.85	0.37–1.93	1.18	0.72–1.93	0.98	0.53–1.81	0.85	0.61–1.19	0.77	0.49–1.21
Daily smoking	0.91	0.27–3.11	1.07	0.13–8.56	1.26	0.36–4.38	2.48	0.68–9.06	0.85	0.36–2.03	0.82	0.24–2.84
Daily use of snuff tobacco	1.06	0.65–1.72	0.47	0.17–1.30	1.27	0.77–2.10	1.46	0.78–2.73	1.09	0.77–1.56	0.84	0.51–1.38

Multivariable logistic regression model analyzed separately with asthma, severe asthma, eczema, severe eczema, AR, and severe AR as outcome and nasal *S. aureus* carriage as main predictor (yes vs. no), adjusted for sex (female vs. male), BMI (≥25 kg/m^2 vs. <25 kg/m^2), use of antibiotics last 3 months (yes vs. no), screen-time on weekdays (≥4 h vs. <4 h), physical activity outside school time (yes vs. no), daily smoking (yes vs no), and daily use of snuff tobacco (yes vs no). OR = Odds ratio, 95% CI = 95% confidence interval. Outcome definitions are listed in Table 1.

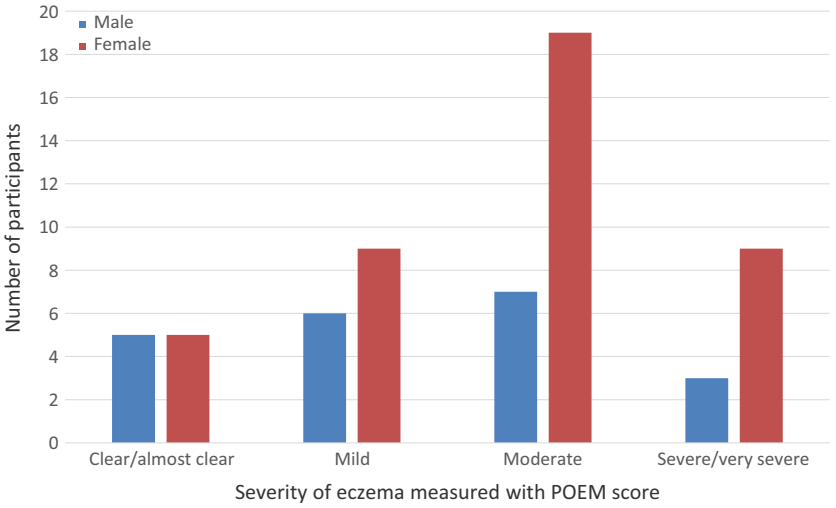

Figure 2 Severity of atopic dermatitis measured with POEM score. POEM scores are 0–2 = clear/almost clear, 3–7 = mild, 8–16 = moderate, 17–24 = severe, 25–28 = very severe. The Tromsø Study Fit Futures 2, n = 63.

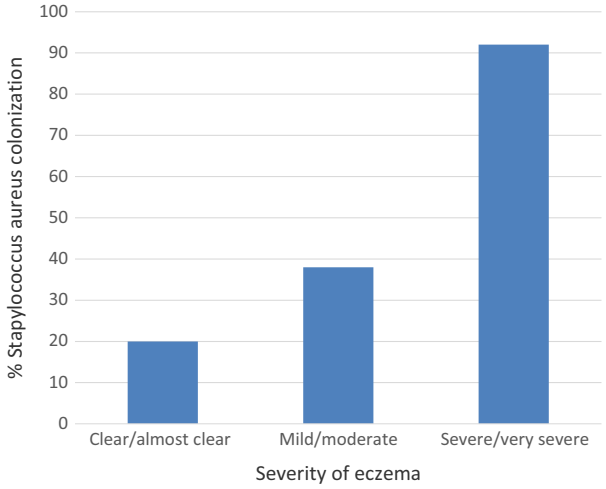

Figure 3 Proportion of *Staphylococcus aureus* carriage on eczematous skin related to severity of eczema graded by POEM score. POEM scores are 0–2 = clear/almost clear; 3–16 = mild/moderate, 17–28 = severe/very severe. The Tromsø Study Fit Futures 2, n = 46.

Discussion

In this large cohort of late adolescents, we found high prevalence of asthma (11.9%), eczema (10.4%), AR (26.0%), and allergic multimorbidity (10.2%). The lifetime prevalence for having any allergic disease was 45.1%. Compared with the Swedish BAMSE study (4), the British IOW study (2), and the German MAS study (3), the prevalence of allergic disease in our population is close to the findings in Sweden and Germany, except for asthma which is lower in Sweden. In the IoW study, there are higher prevalence for asthma, AR, and multimorbidity (2). Variations in prevalence rates may be due to regional differences, but may partially also be due to different outcome definitions. Operational definitions of asthma in recent epidemiological studies are inconsistent (24). We used the same outcome definition for asthma as in the MAS study (3). For eczema and AR, we used the same definitions as in the BAMSE study (4).

We found a female predominance of eczema and multimorbidity. It has been hypothesized that sex hormones play a role in the pathogenesis of allergic diseases (25, 26). Experimental evidence indicates that androgens appear to have immunosuppressive effects, while estrogens are proinflammatory and may increase the susceptibility to atopy. Influence of sex hormones may thus explain the gender difference in our results.

More than half of late adolescents in our study had nasal *S. aureus* carriage. In contrast, only 1/4 of adults aged 30-69 years in a previous population-based study from the same region had nasal *S. aureus* carriage (20). The reason for strikingly higher nasal *S. aureus* carriage among adolescents is not clear. Nasal *S. aureus* carriage was associated with eczema, severe asthma, and severe AR, indicating that staphylococcal carriage may play a role in the pathogenesis of allergic diseases. Specific IgE to *S. aureus* superantigens in the nasal mucosa may induce immunomodulatory effects and a Th2-type eosinophilic inflammation in patients with AR (11, 27). In patients with asthma, superantigen-specific IgE is commonly detected, in particular frequent in patients with severe asthma (6, 28). When we adjusted each allergic disease for the other allergic diseases, only eczema was significantly associated with nasal *S. aureus* carriage, indicating that *S. aureus* carriage is more important for the severity of eczema than asthma and AR. However, asthma, eczema, and AR are closely related diseases that partially share the same genetic predisposition, etiology, and pathogenic mechanisms. As a consequence, adjusting for the other allergic diseases will underestimate the strength of the associations with nasal *S. aureus* carriage. Our epidemiological data do not prove causation, and the observed association could also be the result of reverse causation; inflammation due to allergic disease makes the mucosa more susceptible to *S. aureus* carriage. Many studies suggest that *S. aureus* carriage plays a role in the severity of established allergic diseases. This is supported by our findings, but pathophysiological mechanisms and putative therapeutic or

prophylactic consequences need to be addressed in the future studies.

The role of *S. aureus* skin carriage as a factor contributing to the exacerbation of eczema is well established (8). The majority of participants with eczematous skin carriage were also colonized in the nose, pointing to the nose as the source of *S. aureus* in patients with eczema. However, even though the nose is the most consistent human niche for *S. aureus* carriage, we cannot rule out that *S. aureus* from the skin in some cases was the source of nasal carriage. The role of eczematous skin *S. aureus* carriage in eczema exacerbation was supported by increasing carriage rates with increasing eczema severity in our study. This has been shown in many studies (29, 30), but therapeutic strategies to restore permanent normal skin flora are lacking and may be complicated by high nasal carriage rate of *S. aureus* in patients with eczema and in the general population.

Spirometry showed signs of current obstruction in 11.6% of asthmatic participants, and only around 5% had more than 12% improvement in FEV_1 after inhalation of salbutamol. The poor sensitivity of spirometry to diagnose current asthma is also known from previous studies (31, 32). It may be due to both the intermittent course of asthma but also to good asthma control as nearly 2 of 3 of asthmatic participants were treated with ICS. In line with others (33), we also found that only 1 of 5 of asthmatic participants had increased levels of FeNO > 25 ppb. Furthermore, in a Norwegian study on adolescents with bronchiolitis in infancy, exhaled nitric oxide was related to atopy, but not to asthma (34). Some international guidelines recommend using FeNO in phenotyping airway inflammation and monitoring of severe asthma (33), while the recent international ERS/ATS guidelines on severe asthma suggest that clinicians should not use FeNO to guide therapy in adults or children (35). We found that FeNO > 25 ppb was associated with asthma only in participants with nasal *S. aureus* carriage. A possible explanation for this finding is nasal eosinophilic inflammation due to staphylococcal superantigens. As a consequence, nasal *S. aureus* carriage may contribute to the low specificity of FeNO in asthma diagnosis and disease monitoring.

The main strengths of our study are the school-based approach covering more than 90% of the late adolescents in this age group in the two municipalities, the large sample size with a high participation rate and the combination of both self-reported and objective health measurements. We believe our data represent good estimates of prevalence rates of allergic diseases in this population. However, the cross-sectional design is a limitation in evaluating the observed associations between allergic disease and *S. aureus* carriage. Furthermore, with only one nasal swab, we cannot distinguish between intermittent and persistent *S. aureus* carriage. Measurement of *S. aureus* enterotoxin IgE and Th2 markers was also not available, but could have added information to this study.

Conclusion

Asthma, eczema, and allergic rhinitis are common chronic diseases among adolescents in Northern Norway. Nearly half of the adolescent population has experienced one or more of these diseases by the age of 18–19, and multimorbidity of allergic disease exists in 10% of all adolescents. Allergic disease is associated with *S. aureus* carriage, but its role in the pathogenesis and severity is not established.

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References

1. Hansen T, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985–2008. *Acta Paediatr* 2013: **102**: 47–52.
2. Ziyab AH, Karmaus W, Zhang H, et al. Allergic sensitization and filaggrin variants predispose to the comorbidity of eczema, asthma, and rhinitis: results from the Isle of Wight birth cohort. *Clin Exp Allergy* 2014: **44**: 1170–8.
3. Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015: **26**: 431–7.
4. Ballardini N, Bergstrom A, Wahlgren CF, et al. IgE-antibodies in relation to prevalence and multimorbidity of eczema, asthma and rhinitis from birth to adolescence. *Allergy* 2016: **71**: 342–9.
5. Sintobin I, Keil T, Lau S, et al. Is immunoglobulin E to *Staphylococcus aureus* enterotoxins associated with asthma at 20 years? *Pediatr Allergy Immunol* 2015: **26**: 461–5.
6. Tomassen P, Jarvis D, Newson R, et al. *Staphylococcus aureus* enterotoxin-specific IgE is associated with asthma in the general population: a GA(2)LEN study. *Allergy* 2013: **68**: 1289–97.
7. Bachert C, van Steen K, Zhang N, et al. Specific IgE against *Staphylococcus aureus* enterotoxins: an independent risk factor for asthma. *J Allergy Clin Immunol* 2012: **130**(): e8.
8. Huvenne W, Hellings PW, Bachert C. Role of staphylococcal superantigens in airway disease. *Int Arch Allergy Immunol* 2013: **161**: 304–14.
9. Miller LG, Eells SJ, Taylor AR, et al. *Staphylococcus aureus* colonization among household contacts of patients with skin infections: risk factors, strain discordance, and complex ecology. *Clin Infect Dis* 2012: **54**: 1523–35.
10. Shiomori T, Yoshida S, Miyamoto H, Makishima K. Relationship of nasal carriage of *Staphylococcus aureus* to pathogenesis of perennial allergic rhinitis. *J Allergy Clin Immunol* 2000: **105**: 449–54.
11. Riechelmann H, Essig A, Deutschle T, Rau A, Rothermel B, Weschta M. Nasal carriage of *Staphylococcus aureus* in house dust mite allergic patients and healthy controls. *Allergy* 2005: **60**: 1418–23.
12. van de Kant KD, Klaassen EM, van Aerde KJ, et al. Impact of bacterial colonization on exhaled inflammatory markers in wheezing preschool children. *J Breath Res* 2012: **6**: 046001.
13. Davis MF, Peng RD, McCormack MC, Matsui EC. *Staphylococcus aureus* colonization is associated with wheeze and asthma among US children and young

adults. *J Allergy Clin Immunol* 2015: **135**(): e5.
14. Winther A, Dennison E, Ahmed LA, et al. The Tromso Study: fit futures: a study of Norwegian adolescents' lifestyle and bone health. *Arch Osteoporos* 2014: **9**: 185–96.
15. Hohmann C, Pinart M, Tischer C, et al. The development of the MeDALL core questionnaires for a harmonized follow-up assessment of eleven European birth cohorts on asthma and allergies. *Int Arch Allergy Immunol* 2014: **163**: 215–24.
16. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004: **140**: 1513–9.
17. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013: **169**: 1326–32.
18. Kapande KM, McConaghy LA, Douglas I, et al. Comparative repeatability of two handheld fractional exhaled nitric oxide monitors. *Pediatr Pulmonol* 2012: **47**: 546–50.
19. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012: **40**: 1324–43.
20. Olsen K, Sangvik M, Simonsen GS, et al. Prevalence and population structure of *Staphylococcus aureus* nasal carriage in healthcare workers in a general population. The Tromso Staph and Skin Study. *Epidemiol Infect* 2013: **141**: 143–52.
21. Olsen K, Danielsen K, Wilsgaard T, et al. Obesity and *Staphylococcus aureus* nasal colonization among women and men in a general population. *PLoS ONE* 2013: **8**: e63716.
22. Kock R, Werner P, Friedrich AW, Fegeler C, Becker K. Persistence of nasal colonization with human pathogenic bacteria and associated antimicrobial resistance in the German general population. *New Microbes and New Infect* 2016: **9**: 24–34.
23. Micallef L, Rodgers P. eulerAPE: drawing area-proportional 3-Venn diagrams using ellipses. *PLoS One* 2014: **9**: e101717.
24. Sa-Sousa A, Jacinto T, Azevedo L, et al. Operational definitions of asthma in recent epidemiological studies are inconsistent. *Clin Transl Allergy* 2014: **4**: 24.
25. Almqvist C, Worm M, Leynaert B, For the working group of GALENWPG. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008: **63**: 47–57.
26. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008: **63**: 1418–27.
27. Rossi RE, Monasterolo G. Prevalence of serum IgE antibodies to the *Staphylococcus aureus* enterotoxins (SAE, SEB, SEC, SED, TSST-1) in patients with persistent allergic rhinitis. *Int Arch Allergy Immunol* 2004: **133**: 261–6.
28. Bachert C, Gevaert P, Howarth P, Holtappels G, van Cauwenberge P, Johansson SG. IgE to *Staphylococcus aureus* enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol* 2003: **111**: 1131–2.
29. Pascolini C SJ, Pecetta S, Bordignon V, et al. Molecular and immunological characterization of *Staphylococcus aureus* in pediatric atopic dermatitis: implications for prophylaxis and clinical management. *Clin Dev Immunol* 2011: **2011**: 718708. doi: 10.1155/2011/718708.
30. Gilani SJK, Gonzalez M, Hussain I, Finlay AY, Patel GK. *Staphylococcus aureus* re-colonization in atopic dermatitis: beyond the skin. *Clin Exp Dermatol* 2005: **30**: 10–3.
31. Lang AM, Konradsen J, Carlsen KH, et al. Identifying problematic severe asthma in the individual child – does lung function matter? *Acta Paediatr* 2010: **99**: 404–10.
32. Backer V, Sverrild A, Ulrik CS, Bodtger U, Seersholm N, Porsbjerg C. Diagnostic work-up in patients with possible asthma referred to a university hospital. *Eur Clin Respir J* 2015: **2**: doi: 10.3402/ecrj.v2.27768.
33. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011: **184**: 602–15.
34. Mikalsen IB, Halvorsen T, Oymar K. Exhaled nitric oxide is related to atopy, but not asthma in adolescents with bronchiolitis in infancy. *BMC Pulm Med* 2013: **13**: 66.
35. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014: **43**: 343–73.